California Institute for Regenerative Medicine:
Standards Working Group

Ethical and Scientific Oversight of Human Embryonic Stem Cell (hESC) Research

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Embryonic Stem Cell Oversight (ESCRO) Committee & Institutional Review Boards (IRBs)

1. Goals for review of hESC research:

- The highest ethical and scientific standards in the conduct of hESC research

- High standards will promote public confidence

- Thorough, efficient, and avoid duplication of effort

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2. Methods:

- Potential conflicting CA hESC laws
- Flexibility to avoid locking CIRM or institutions into a "strict constructionist" NAS model when there may be multiple appropriate models to achieve goals

3. A unique opportunity to create a unified system of protections:

- CIRM hESC laws
- CA hESC laws

Review Requirements

- California Law & CIRM responsibilities
- Federal regulations
- National Academies of Science guidelines

CA Law & Federal Regulations

- CA Health & Safety (H&S) Code 125119:

  "**All research projects involving the derivation or use of [hESC] shall be reviewed and approved by an [IRB] that is established in accordance with federal regulations, including [45 CFR 46], prior to being undertaken**."

  – Must apply guidelines developed by the CA Department of Health Services (DHS) on or before 1/1/05.

  – IRB must review at least once per year

  – IRBs that conduct such review must report annually specific information to the DHS.

CA Law & CIRM

- CIRM has the authority to create different review requirements for CIRM sponsored research [CA H&S Code 125290.35]

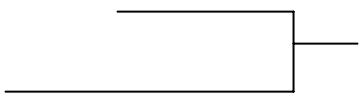
- Potentially creates 2 classes of hESC research law:
  - CIRM sponsored research
  - Non-CIRM sponsored research

- Places institutions who conduct hESC research with and without CIRM funds in a challenging position

- Opportunity to create flexibility, harmonize requirements, and ensure consistent standards

IRBs: Regulations & Laws

- IRBs created to protect the rights and welfare of human research subjects as defined by Federal regulations and local laws
- Governed by HHS & FDA regulations, State laws, and institutional policies
- HHS Assurances: Institutions commonly agree to apply the same standards to all human research
- Minimum of 5 members
  - Sufficient scientific expertise
  - Diversity of race, gender, and cultural background
  - Sensitivity to community issues
  - At least one non-scientist
  - At least non-affiliated



What does an IRB do?

- **Reviews research proposals**
- **Applies ethical standards:**
  - Beneficence: Risk:benefit analysis
  - Justice: Equitable selection of subjects
  - Respect for persons: Dignity and autonomy of subjects/Informed consent
- **Applies legal standards**

Beneficence

1. Risks to subjects are minimized:

   (a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

   (b) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

Justice

- Selection of subjects is equitable.
  - Assess the purpose and setting of the research in order to
  - address special issues of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

Federal Definition of a Human Subject

A ***living individual*** about whom an investigator (whether professional or student) conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information.

- *45 CFR 46.102(f)*

Federal Regulations: 45 CFR 46 Subpart B

- Fetus: “the product of conception from implantation until delivery”

- The Federal definition of human research subject does not include:
  - blastocysts that are not implanted or
  - blastocysts or gametes without identifiers that could be linked back to the donors.

- Therefore, such material is not subject to Federal IRB regulatory oversight

Laboratory Research

- Do the HHS regulations cover laboratory research on embryos created for research or derived from IVF prior to implantation?
  - No. HHS IRB regulations do not cover such research so long as the product is not given to a living individual for research purposes or contain identifying information of a living individual.
  - Therefore, such material used in hESC research does not fall within IRB purview under the Federal regulations.
- Are cell lines developed from stored material prior to implantation covered by HHS regulations?
  - No, so long as the product is not given to a living individual for research purposes or contain identifying information of a living individual.

NAS Guidelines: ESCRO Committees

- Create a local ESCRO committee that will review all hESC research at an institution
- Intended guidelines for the entire USA
- Did ***not*** use CA as a model for research oversight where IRB review of all hESC research is required by law
- Structured the ESCRO membership similar to IRBs and highlighted similar responsibilities, understanding that hESC research, including non-human subject laboratory research, should have ethical and scientific oversight
- Ensure an IRB type review occurred when federal IRB human research regulations for IRB review do not apply and local law does not require IRB review

ESCRO Responsibilities

- Provide oversight for all issues related to derivation and use of hESCs
- Review and approve the scientific merit of hESC proposals
- Review compliance of all in-house hESC research with applicable regulations/guidelines
- Maintain hESC registries and account for all hESC research
- Education

NAS Guidelines: Duplication of Effort

- Addressed overlapping duties and potential for local flexibility:

"A pre-existing committee could serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to perform the various roles described in this report."

"…Care should be taken that the ESCRO committee does not duplicate or interfere with the proper functions of an IRB… the functions of IRBs and ESCRO committees are distinct and should not be confused."

Comparison of ESCRO and IRB Membership and Duties as Defined by NAS-IOM Guidelines and Federal Regulations

	ESCRO	**IRB**
MEMBERSHIP		
Scientific expertise	Yes	Yes
Medical expertise	Yes	Yes, for biomedical research only
Ethics expertise	Yes	Not specifically but implied
Community	Yes	Yes (non-affiliated)
Diversity of membership (race, gender, culture)	Not required	Yes
DUTIES		
Scientific evaluation	Yes	Yes, as the research design impacts the rights & welfare of the subjects
Ethics	Yes	Yes
Risk:Benefit analysis	Yes	Yes
Informed consent	Yes	Yes
Compliance	Yes	Yes
Education	Yes	Yes
Derivation of cells	Yes	Yes
Accounting of cells and research	Yes	To a limited extent, yes, as they must account for all research.
Review of all hESC research	Yes (IOM Guidance)	Yes & No (CA law requires IRB review of all hESC research.. CIRM could determine otherwise for CIRM funded research.)

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Possible Institutional-CIRM Approaches

- **Plan A**: ESCRO and IRB *[Two local committees with overlapping duties and responsibilities]*
- **Plan B**: hESC Scientific Review Committee (SRC) and IRB *[Two local committees with separate duties requiring cooperation, modeled on NCI Comprehensive Cancer Center requirement to perform a scientific evaluation of cancer center research]*
- **Plan C**: IRB that includes an ESCRO Committee *[One local committee, requires augmenting IRB membership for a limited number of protocols]*
- **Plan D**: A central ESCRO Committee implemented by the State similar to the NIH Recombinant DNA Advisory Committee (RAC)

Possible Institutional-CIRM Approaches

	Plan A		Plan B		Plan C	PLAN D
Responsibilities	**ESCRO**	**IRB**	**hESC SRC**	**IRB**	**ESCRO-IRB Hybrid**	**CA State ESCRO**
Ethics	Yes	Yes	No	Yes	Yes	
Science	Yes	Limited	Yes	Limited	Yes	
Risk : Benefit analysis	Yes	Yes	Limited	Yes	Yes	
Informed consent	Yes	Yes	No	Yes	Yes	
Recruitment	Yes	Yes	No	Yes	Yes	
Payment/undue influence	Yes	Yes	No	Yes	Yes	
Accounting of cells/projects	Yes	Yes	Yes	No	Yes	
Derivation issues	Yes	Yes	Yes	No, except in clinical research	Yes	
Provenance/procurement of cells	Yes	Yes	Yes, scientific issues	Yes, ethical issues	Yes	
Education	Yes	Yes	Yes	Yes	Yes	

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Questions

1. Will some institutions want to create a single unified protection system for all hESC research at the institution that will address both CIRM funded and non-CIRM funded research, similar to current HHS human research assurances?

2. Will a “strict constructionist” interpretation of NAS-IOM guidelines by CIRM unduly limit institutional flexibility in the creation of a unified and single system of protections?

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Questions, continued

3. Since CIRM is exempt from CA H&S code requirements for IRB review of all hESC research, should CIRM create regulations that avoid the possibility of a 2 class system of review/oversight of hESC research?

   a. Institutions that receive both CIRM and non-CIRM funds may have two distinct and competing sets of oversight requirements that may also overlap in decision making responsibilities:

      (1) CIRM rules for CIRM sponsored research

      (2) CA H&S code 125119 for non-CIRM sponsored research

   b. A two class system could result in duplicative functions, wasted resources, and result in discordant determinations on the same issues ultimately undermining the integrity of the system and resulting in a break down in trust of the research community.

Questions, continued

4. Is there room for flexibility in crafting CIRM requirements so that review standards:

   a. enable institutions to achieve the important goals of only conducting research that meets the highest ethical and scientific standards and builds public confidence, and

   b. allows institutions to meet the intent of the NAS guidelines through various local committee structures that maximize resources and minimize duplication of effort while allowing institutions to create the best local committee methodology to achieve the goals?

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